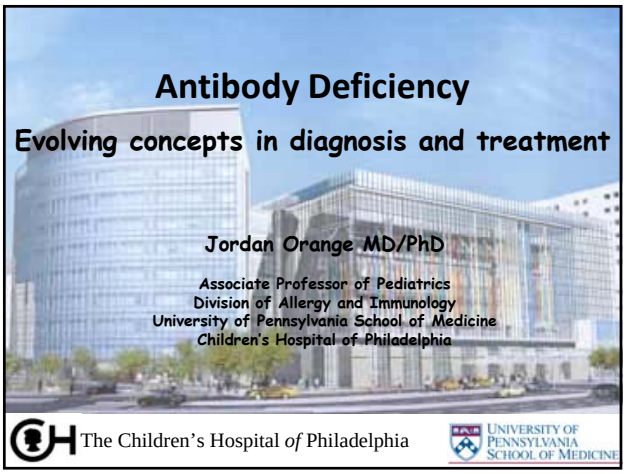

Disclosure Slide

Employment
- Children's Hospital of Philadelphia

Financial Interests
- Consultant to Baxter, CSL, Talecris, Genentech, IBT

Research Interests
- NIH-NIAID, Baxter Bioscience

Organizational Interests
- AAAAI, ACAAI, AAI, CIS, IDF

Gifts
- Nothing to Disclose

Other Interests
- Research grants review committee – Octapharma USA

Learning Objectives

Upon conclusion of this session, participants should be able to:

- Consider increasingly complex numbers of primary immunodeficiency diagnoses related to antibody deficiency
- Discuss the prescribed therapeutic options available for treatment of antibody deficient patients
- Explain the optimization of IVIG therapy for antibody

Outline: Evolving concepts in diagnosis and treatment

- Diagnostic categories
- Antibiotic prophylaxis
- Immunoglobulin replacement
  - Intravenous Optimization
  - Subcutaneous
- Consideration of complex pathogenesis using GWAS

IUIS defines 155 PIDDs

Primary immunodeficiencies: 2009 update

International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies: Luigi D. Notarangelo, MD,[a] Alain Fischer, MD,[b] and Raif S. Geha, MD[a] (Cochairs); Jean-Laurent Casanova, MD,[c] Helen Chapel, MD,[d] Mary Ellen Conley, MD,[e] Charlotte Cunningham-Rundles, MD, PhD,[f] Amos Etzioni, MD,[g] Lennart Hammarström, MD,[h] Shigeaki Nonoyama, MD,[i] Hans D. Ochs, MD,[j] Jennifer Puck, MD,[k] Chaim Roifman, MD,[l] Reinhard Seger, MD,[m] and Josiah Wedgwood, MD, PhD[n] *Boston, Mass, Paris, France, New York, NY, Oxford, United Kingdom, Memphis, Tenn, Haifa, Israel, Stockholm, Sweden, Tokorozawa, Japan, Seattle, Wash, San Francisco, Calif, Toronto, Ontario, Canada, Zurich, Switzerland, and Bethesda, Md*

64 in the majority affect antibodies

Do we need 64 individual guidelines?

Phenotypic categorization of antibody deficiency

- B cells
  - Present or absent
- IgG quantity
  - Absent, low, normal
- IgG quality
  - Absent, low, normal

As derived from: Orange, et. al., JACI 2006 S525

As proposed in Stiehm, Orange and Ballow, advances in pediatrics, in press

Category	B cells	IgG quantity	IgG quality (antigen-specific antibody)	Diagnostic examples	Ig replacement therapy	Cessation of therapy for reevaluation
I	Absent	Absent	Absent	Agammaglobulinemia SCID	Absolute indication – provide immediately	Inappropriate
II	Present	Low	Low	Hyper IgM CVID NEMO deficiency (subset)	Absolute indication, provide after firm diagnosis	Inappropriate if molecularly defined otherwise a single lifetime trial of cessation is appropriate
III	Present	Normal	Low	Specific Antibody Deficiency NEMO deficiency (subset) Subclass deficiency with specific antibody defect	Provide if diagnosis is firm or if infections persist	Single trial appropriate only if diagnosis is not related to a specific genetic defect
IV	Present	Low	Normal	Transient hypogammaglobulinemia of infancy Primary hypogammaglobulinemia	Provide when clinically indicated	Reassess if indicated with a single trial
V	Present	Normal, but IgG subclass deficient	Normal	IgG1, IgG2, or IgG3 subclass deficiency	Provide when clinically indicated	Reassess if indicated with a single trial
VI	Present	Normal	Normal	Recurrent infection	As adjunct therapy where indicated	As appropriate

Stiehm, Orange and Ballow, advances in pediatrics, in press

Clinical Immunology (2010) 135, 255–263

available at www.sciencedirect.com

Clinical Immunology

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Use of intravenous immunoglobulin and adjunctive therapies in the treatment of primary immunodeficiencies

A working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology

Pierre L. Yong [a,b], John Boyle [c], Mark Ballow [d], Marcia Boyle [c], Melvin Berger [e], Jack Bleesing [f], Franciso A. Bonilla [g,h], Javier Chinen [i], Charlotte Cunninghamm-Rundles [j], Ramsay Fuleihan [k], Lois Nelson [l], Richard L. Wasserman [m], Kathleen C. Williams [n], Jordan S. Orange [o,*]

AAAAI Working Group Report

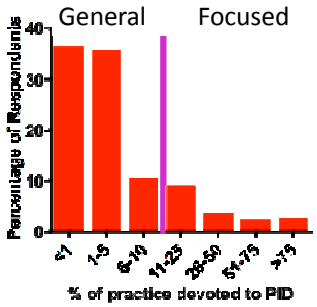
- Web-based survey
- E-mail invitation to 3,000 AAAAI members
- 405 unduplicated respondents
- Data collection period of ~4mos
- 13.5% response rate

Yong, et. al. Clin. Immunol. 2010 235:155

- Parallel survey was performed of ESID
  - Response rate 28.5%

AAAAI Respondent Characteristics

- 80% currently treat patients with PIDD
  - Most common diagnosis treated is CVID



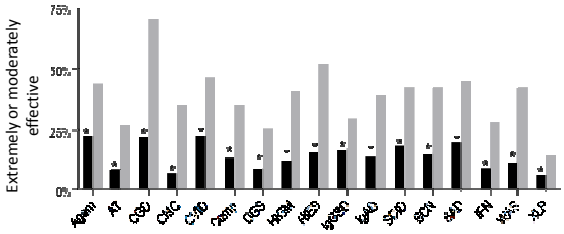
Yong, et. al. Clin. Immunol. 2010, 135:255

Antibiotics

Providing an advantage over the environment

US Agricultural research service

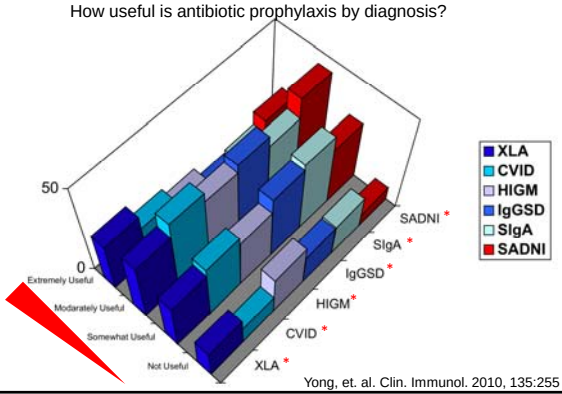
Prophylactic antibiotics for PIDD



Yong, et. al. Clin. Immunol. 2010, 135:255

Which antibody deficiencies are being treated with propylactic antibiotics

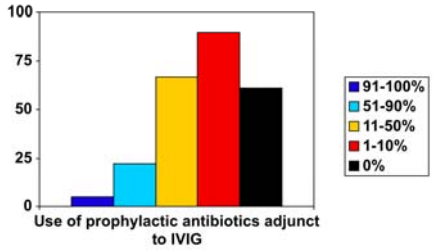
How useful is antibiotic prophylaxis by diagnosis?



Yong, et. al. Clin. Immunol. 2010, 135:255

Prophylactic antibiotics + IVIG

What % of patients do you recommend IVIG and prophylactic antibiotics?



Yong, et. al. Clin. Immunol. 2010, 135:255

Polyclonal Immunoglobulin

- From pooled plasma from 1000s of donors
  - **Ensures broad specificity**
  - US FDA recommends >15,000, but <60,000 pooled donors

•Sourced from
-Commercial plasma collection centers

US IGIV products must be manufactured from plasma donated in the US




Polyclonal immunoglobulin preparations

- **IGIV - immunoglobulin (IG), intravenous (IV)**
  - **(IVIG)**
- IGIM - immunoglobulin (IG), intramuscular (IM)
  - (IMIG)
- **IGSC - immunoglobulin (IG), subcutaneous (SC)**
  - **(SCIG)**
- Hyperimmune immunoglobulins
  - IM (tetanus) and IV (CMV)

US IVIG preparations (7)

Product	Form	Stabilizer sugar	IgA (µg/ml)	Osm (mOsm/kg or L)	Sodium (mg/ml)	Storage	Manuf
Carimune	Lyoph.	Sucrose	trace	768 (12%)	<2.4	RT (24m)	CSL
Flebogamma	5% liq	Sorbitol	<50	240-370	?	RT (24m)	Griffols
Gammagard liquid	10% liq	Glycine	37	240-300	"none added"	RT (6m) 4° (36m)	Baxter
Gammagard SD	Lyoph.	Glucose	<2.2	1250 (10%)	8.5	RT (24m)	Baxter
Gammunex	10% liq	Glycine	46	258	trace	RT (9m) 4° (36m)	Talecris
Octagam	5% liq	Maltose	<200	310-380	<0.7	RT (24m)	Octaph
Privigen	10% liq	Proline	<25	240-440	trace	RT (24m)	CSL

US SCIG and IMIG preparations

Product	Approved Route	Form	Stabilizer /sugar	IgA (µg/ml)	Sodium (mg/ml)	Storage	Manuf
Gammastan	**IM**	~16% liquid	Glycine	?	3.0	4°	Talecris
Vivaglobin	**SC**	16% liquid	Glycine	1700	<3.2	4°	CSL
Hizentra	SC	20% liquid	Proline	<50	"trace"	Room Temp	CSL

IVIG product selection

- **Sucrose** (Caramune)
  - avoid in renal risks
- **Glucose** (Gammagard SD)
  - avoid in diabetes
- **Sodium** (Gammagard SD - 0.85%, Caramune)
  - avoid in infants and cardiovascular risks
- **High Osm** (Gammagard SD)
  - avoid in infants and cardiovascular risks
- **Fluid load** (5% preperations – Flebogamma, Octagam)
  - avoid in water restriction, caution in infants.
- **Amino acids** (Glycine – Gammunex/Gammagard Liq) (Privigen-Proline)
  - avoid in specific reactivity or certain metabolic disorders
- **IgA** (all except Gammagard SD)
  - avoid in patients with history of reaction

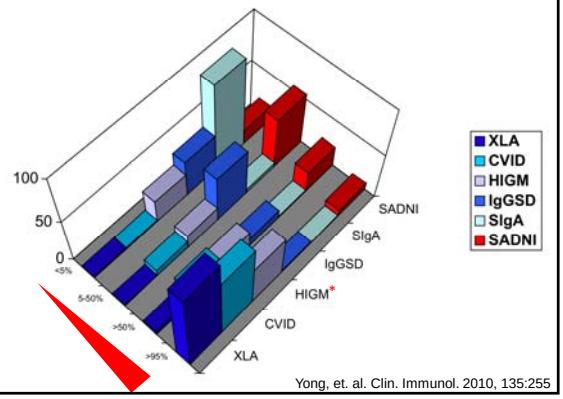
ONLY 2 STUDIES DOCUMENT HEAD-TO-HEAD COMPARISONS

- Gammunex vs Gammimune N in PIDD, Gammune vs Iveeegam in KD

- Subcutaneous therapy- Characteristics may be less relevant

Which antibody deficiencies are being treated with IVIG

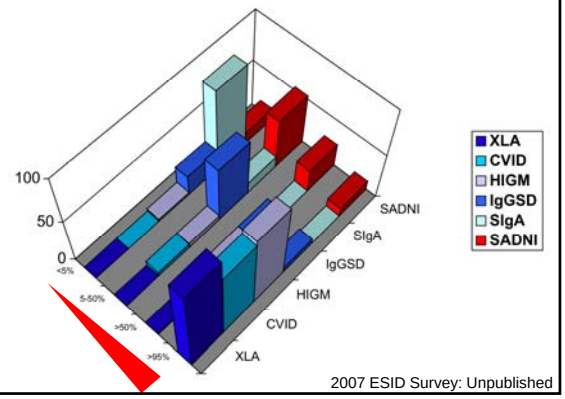
What % **AAAAI** physician of patients are recommended for IVIG therapy?



Yong, et. al. Clin. Immunol. 2010, 135:255

Which antibody deficiencies are being treated with IVIG

What % of **ESID** physician patients are recommended for IVIG therapy?

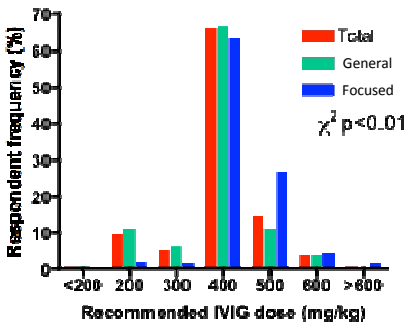


2007 ESID Survey: Unpublished

Optimizing IVIG usage in PIDD

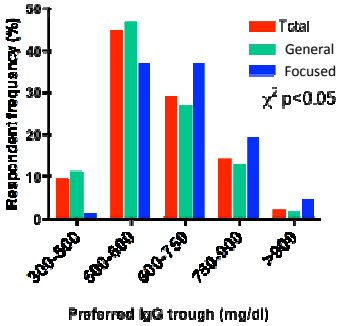
IVIG dosing for PIDD by Allergists

What is the usual initial recommended IVIG dosage?



Yong, et. al. Clin. Immunol. 2009, Epub Nov 13

What pre-infusion IgG level do Allergists target?



Yong, et. al. Clin. Immunol. 2009, Epub Nov 13

The “biological” trough

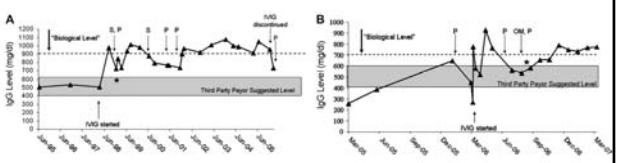


FIG 1. IgG trough levels in patients A and B before, during, and after initiating IVIG therapy and associated infection history. *Time at which our practice assumed the care of this patient. *S*, Acute sinusitis; *P*, pneumonia; *OM*, otitis media.

Bonagura, et. al. J. Allergy Clin. Immunol. 122:210-211

IgG trough levels: a meta analysis

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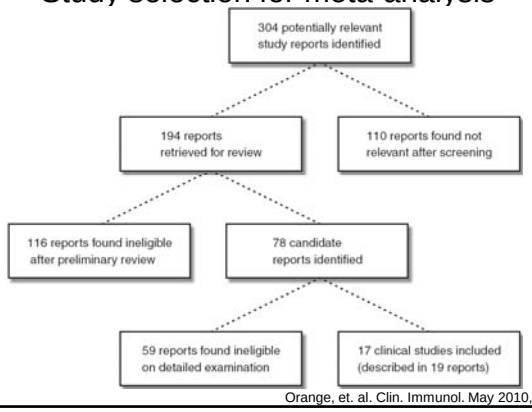
Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies

Jordan S. Orange [a,*], William J. Grossman [b], Roberta J. Navickis [c], Mahlon M. Wilkes [c]

[a] Division of Allergy and Immunology, Children's Hospital of Philadelphia, Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
[b] Biotherapeutics, Baxter Healthcare Corporation, Deerfield, IL, USA
[c] Hygeia Associates, Grass Valley, CA, USA

Study selection for meta-analysis



Orange, et. al. Clin. Immunol. May 2010, ePub

Studies included in meta-analysis

Study	Design	Region	IVIG Product or Supplier	Age[a], y	% Male
Ammann et al, 1982 [29]	P	US	Cutter	32.2 (1.5-63)	79.4
Schiff et al, 1984 [30]	P	US	Intraglobin	17 (3.5-29)	75.0
Roifman et al, 1987 [4-6]	C-RCT	Canada	Sandoglobulin	24[b] (7-50)	66.7
Liese et al, 1992 [7]	R	Germany	Unspecified	2.3 (2-5)	100.0
Quartier et al, 1999 [14]	R	France	LFB, Sandoglobulin or Endobulin	3.0 (0.6-9.7)	100.0
Chapel et al, 2000 [31]	C-RCT	Sweden and UK	Endobulin	44 (18-67)	33.3
Plebani et al, 2002 [20]	R	Italy	Unspecified	3.5 (0.3-17)	100.0
Aghamohammadi et al, 2004 [22]	R	Iran	Unspecified	5.2 (0.8-14.1)	100.0
Berger and Pinciaro, 2004 [32]	P	US	Flebogamma 5%	38.2 (14.0-74.0)	60.8
Ochs and Pinciaro, 2004 [33]	P	US	Octagam	31 (6-74)	60.9
Bayrakci et al, 2005 [28]	R	Turkey	Unspecified	5.1[b] (0.8-13.9)	84.8
Church et al, 2006 [24]	P	US	Gammagard Liquid 10%	34[b] (6-72)	46.0
Pourpak et al, 2006 [23]	R	Iran	Sandoglobulin or Nordimmune	8.1 (2.5-16.0)	53.8
Berger, 2007 [34]	P	US	Flebogamma 5% DIF	38.9 (15.0-75.0)	63.0
Berger et al, 2007 [35]	P	US and Canada	Carimune NF Liquid	32 (4-66)	69.0
Krasovec et al, 2007 [36]	P	Argentina	Inmunoglobulina G Endovenosa UNC	10.1 (2-18)	70.0
Stein et al, 2009 [25]	P	US and Europe	Privigen	28 (3-69)	57.5

Abbreviations: C-RCT, crossover randomized controlled trial; IVIG, intravenous immunoglobulin; P, prospective; R, retrospective.
[a]Mean (range) at baseline except as otherwise indicated
[b]Median; assumed equal to mean for classification of mean age as < 18 year vs. [c] 18 years

Orange, et. al. Clin. Immunol. May 2010, ePub

Summary of studies

- Mean patients per study = 34
- 49% CVID, 37% XLA
- Pneumonia diagnosed by CXR and hospitalization (1), unspecified (10), or specifically as “bacterial pneumonia” (6)

Orange, et. al. Clin. Immunol. May 2010, ePub

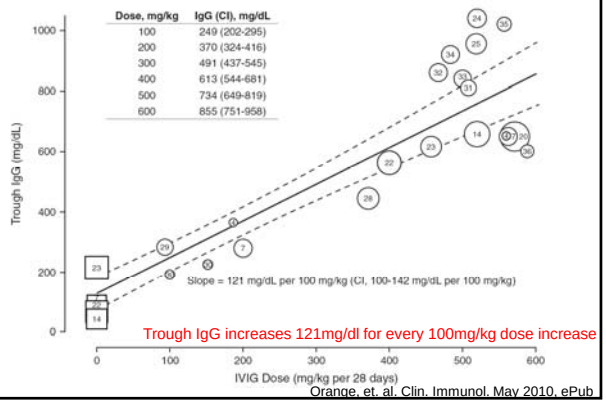
Types of PIDD included in Meta-analysis

Study	CVID	XLA	AGG	HIM	SD	Other	Total
Ammann et al, 1982 [29]	24	7		3			34
Schiff et al, 1984 [30]	12	2		2			16
Roifman et al, 1987 [4-6]	10	2					12
Liese et al, 1992 [7]		29					29
Quartier et al, 1999 [14]		31					31
Chapel et al, 2000 [31]	18				10	2[e]	30
Plebani et al, 2002 [20]		73					73
Aghamohammadi et al, 2004 [22]		5	18				23
Berger and Pinciaro, 2004 [32]	37	12	1	1			51
Ochs and Pinciaro, 2004 [33]	28	13		2	1	2[b]	46
Bayrakci et al, 2005 [28]	20	19		7			46
Church et al, 2006 [24]	22	5		1	1	32[c]	61
Pourpak et al, 2006 [23]	26						26
Berger, 2007 [34]	35	10				1[d]	46
Berger et al, 2007 [35]	32	10					42
Krasovec et al, 2007 [36]	10	14	1[e]			5[f]	30
Stein et al, 2009 [25]	59	21					80
Total	333	253	20	16	12	42	676

Abbreviations: AGG. agammaglobulinemia; AT, ataxia telangiectasia; CVID, common variable immunodeficiency; HIM, hyper-IgM; PIDD, primary immunodeficiency disease; SD, subclass deficiency; XLA. X-linked agammaglobulinemia.
[a]Specific antibody deficiency [b]One each hypogammaglobulinemia and functional immunodeficiency
[c]19 hypogammaglobulinemia; 10 unspecified PIDD; one each AT, SCID, and hyper-IgE syndrome; [d]AT with hypogammaglobulinemia
[e]Autosomal recessive; [f]4 AT; one hyper-IgE syndrome

Orange, et. al. Clin. Immunol. May 2010, ePub

Relation of IgG dose to trough level

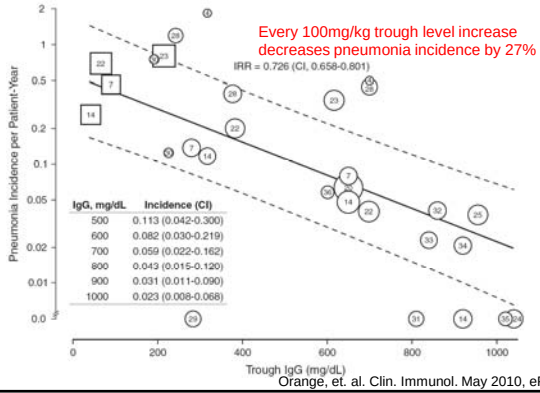


Trough IgG increases 121mg/dl for every 100mg/kg dose increase

Orange, et. al. Clin. Immunol. May 2010, ePub

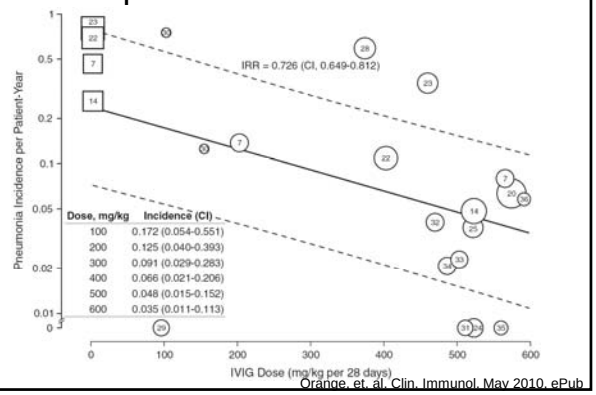
Relation of IgG trough level to pneumonia incidence

Every 100mg/kg trough level increase decreases pneumonia incidence by 27%



Orange, et. al. Clin. Immunol. May 2010, ePub

Relation of IVIG dose to pneumonia incidence



Orange, et. al. Clin. Immunol. May 2010, ePub

Meta-Analysis conclusion

- Trough IgG increases 121mg/dl for every 100mg/kg dose increase
- Every 100mg/kg trough level increase decreases pneumonia incidence by 27%
  - No threshold identified up to 1000mg/dl trough (where data end)
- Experience underscores the need to better define studies in PIDD patients
  - Standard definitions for infections and consistent application
  - Consistent reporting of endpoints relevant to therapy

Orange, et. al. Clin. Immunol. May 2010, ePub

Original article

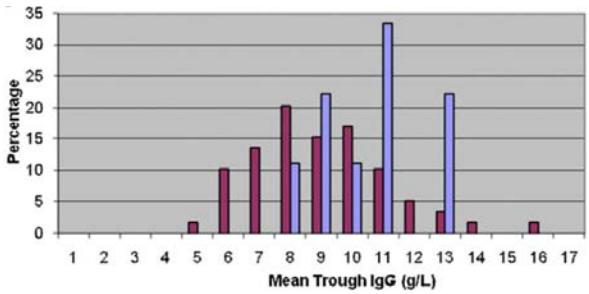
Infection outcomes in patients with common variable immunodeficiency disorders: Relationship to immunoglobulin therapy over 22 years

Mary Lucas, BSc,[a-d] Martin Lee, BA, PhD,[c] Jenny Lortan, MBBS, PhD,[b-d] Eduardo Lopez-Granados, MD, PhD,[a-d] Siraj Misbah, MBBS,[a-d] and Helen Chapel, MA, MD[a-d] *Oxford, United Kingdom, and Los Angeles, Calif*

J. Allergy and Clin. Immunol 2010 125:1354-60

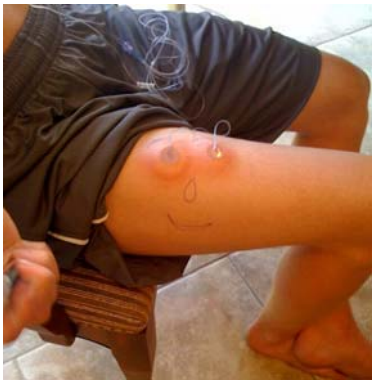
90 CVID – 8891 patient months of data
15 XLA – 1152 patient months of data

IgG trough required to be infection free



Blue XLA Red CVID

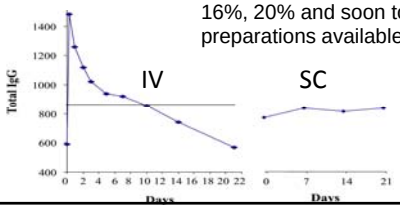
Subcutaneous Immunoglobulin (SCIG)



IV vs. SC replacement

- Therapeutically equivalent to IV for PI[1]
- Less systemic adverse events with SC[1,2]
- More local effects for SC[1,2]
- More stable serum IgG levels for SC[1,3]
  - AUC issue
- More frequent infusion for SC
- Improved quality of life for SC[4]

16%, 20% and soon to be 10% preparations available



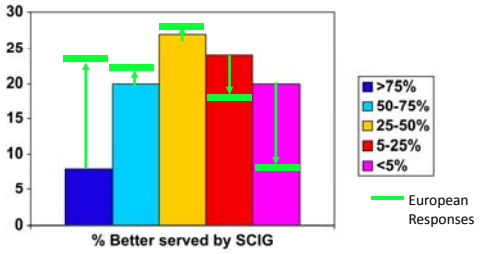
[1]Chapel, H.M., et. al. J. Clin. Immunol 2000 20:94

[2]Gardulf, A., et. al. Lancet 1995 345:365

[3]Berger, M., Clin Immunol. 2004 112:1

[4]Gardulf, A., et. al. J. Allergy Clin. Immunol 2994 114:936

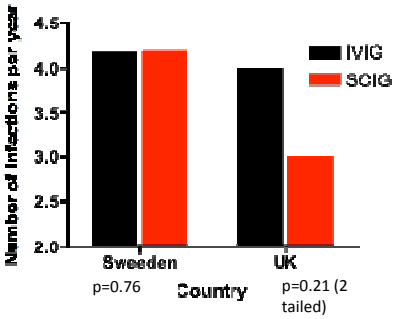
Will SCIG serve patients better than IVIG



Yong, et. al. Clin. Immunol. 2010, 135:255

IV vs SC replacement

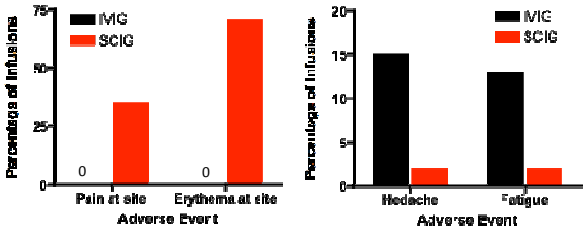
2 year crossover trial



Chapel, H.M., et. al. J. Clin. Immunol 2000 20:94

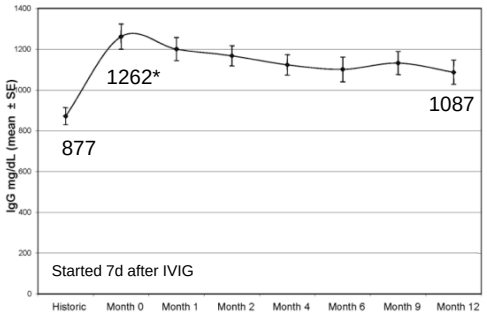
IV vs SC replacement

2 year crossover trial



Chapel, H.M., et. al. J. Clin. Immunol 2000 20:94

Higher sustained IgG level with SCIG dosing at 137%



Virtue Trial – South. Med. J 2010.

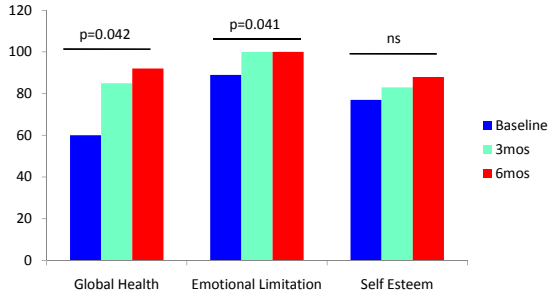
Who Are Candidates for SCIG?

Patients with:

- Adverse Events with IVIG
- IV access problems
- A desire for independence from IV infusion
  - Either hospital or home based
- Difficulty in access to nursing care or medical facilities

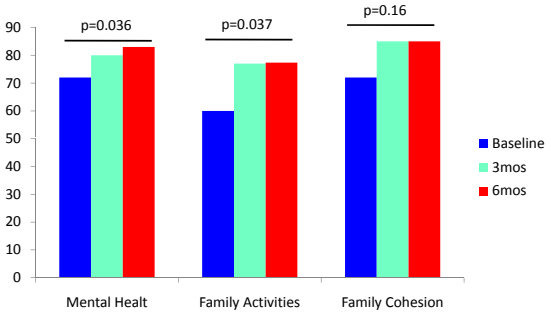
*Hagan, et. al. J. Clin Immunol 2010 ePub

Benefits for Pediatric Patients



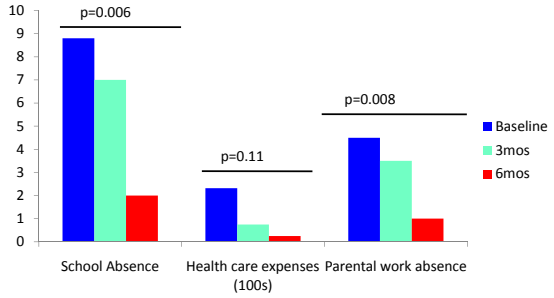
Fasths and Nystrom, J. Clin. Immunol 2008 28:370

Benefits for Parents



Fasths and Nystrom, J. Clin. Immunol 2008 28:370

Health care utilization



Fasths and Nystrom, J. Clin. Immunol 2008 28:370

SCIG: Infusion sites and Time

- Consider patient tolerance, and lifestyle
- A typical infusion lasts 1 – 3 hours
- For a shorter time, use more sites
- for fewer sites, take more time
- US-FDA labeling recommends no more than 15ml/site
  - Many patients tolerate significantly more
- Encourage rotation of SCIG sites
- Evaluate sites over time
- 20% SCIG has better local tolerability than 16% SCIG*

*Hagan, et. al. J. Clin Immunol 2010 ePub

Conclusions

- Antibody deficiency diagnosis needs to evolve to comprehensively cover expanding etiologies of PIDD
  - Phenotypic categories
- Despite specific data, antibiotic usage is commonly employed in antibody deficiency
  - Majority of immunologists use it as an adjunct to IVIG in at least some patients
- Optimization of Ig replacement regimens
  - New data for trough levels at 1000mg/dl
- SCIG equivalent with advantages for the right patient